REMARKS

Applicants submit this Amendment in response to the Office Action mailed July 26, 2000. With entry of this Amendment, claims 1-20 are pending in the application. Support for new claims 19 and 20 may be found throughout the specification. For example, support for claim 19 may be found in originally filed claim 14, and support for claim 20 may be found at p. 16. By this amendment, no new matter is added to the application. Entry of these amendments is respectfully requested. Applicants respectfully request reconsideration of the present application in view of the above amendments and accompanying remarks.

Abstract of the Disclosure.

The Examiner alleges that the specification does not contain an abstract that is in compliance 37 C.F.R. § 1.72(b) and requests, therefore, that Applicants submit an abstract on a separate sheet. Enclosed herewith is a new sheet entitled "ABSTRACT OF THE DISCLOSURE." With entry of this abstract, Applicants submit that the application is now in compliance with 37 C.F.R. § 1.72(b).

Patentability under 35 U.S.C. § 112, First Paragraph.

Claims 1-18 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not supported by an adequate written description. More specifically, the Examiner alleges that the instant claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the present application was filed.

Applicants respectfully traverse the stated grounds of rejection and submit that the specification provides an adequate written description so as to comply with the requirements of 35 U.S.C. § 112, first paragraph.

The instant claims are generally directed to methods of producing a peptide or protein expression library (claims 1-10); expression libraries produced by the method of claims 1-10 (claim 11); DNA molecules containing DNA sequences encoding peptides or proteins for use in expression libraries and vectors containing such DNA sequences (claims 12 and 13, respectively); methods for identifying and/or purifying library members (claim 14) and target-binding peptides or proteins (claims 15-16); methods of assaying for the presence of target molecules (claim 17); and bifunctional molecular probes (claim 18).

With the present amendment, the claims, thus, relate to methods of producing peptide or protein expression libraries wherein a population of nucleotide sequences is expressed. The resulting peptides or proteins encoded by their nucleotide sequences are screened to identify proteins or peptides of interest having a desired feature, such as the ability to bind a selected ligand. Such peptides or proteins are specifically associated with DNA encoding them through covalent binding of the protein to the encoding DNA. By virtue of this covalent binding, the DNA that uniquely encodes the peptide or protein of interest may be recovered and subjected to subsequent characterization such as PCR amplification and/or nucleotide sequencing.

Applicants respectfully submit that the instant specification does in fact provide an adequate written description of the peptides or proteins of the present invention for use according to the present invention. Accordingly, the skilled artisan is provided with a number of exemplary proteins possessing the claimed functional property. Applicants point out, however, that the invention is not restricted, as the Examiner asserts, to any particular cis-acting protein or fragment thereof. Rather, the invention is directed generally to methods of producing libraries that express peptides or protein and that makes use of the property of a subset of proteins that bind covalently to their own coding DNA.

In this regard, it is urged that one skilled in the art would not require any additional written description beyond the disclosure of the present specification in order to identify peptides or proteins as according to the presently claimed invention. Furthermore, the invention is not restricted to the use of any particular peptide or protein but, rather, to a more general property of a broader group of proteins. Thus, it is respectfully submitted that it is improper to restrict Applicants to the specific proteins presented in the Examples.

In view of these remarks and the written description provided by Applicants' disclosure, Applicants respectfully request reconsideration and withdrawal of the present basis for rejection under § 112, first paragraph.

Patentability under 35 U.S.C. § 112, Second Paragraph.

Claims 1-18 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Each of the Examiner's specific bases for rejection is addressed herein, *seriatim*.

A) The Examiner objects to the recitation of "a diverse population" and the term "protein:DNA" in claim 1. More specifically, the Examiner alleges that it is unclear whether "diverse population" refers to the same family of proteins or, rather, proteins of different structures, functions, etc.

Applicants respectfully disagree with these bases for objecting to the present claim language and submit that "diverse population" as it is used in the present claims may relate to proteins that are diverse in any respect. Thus, the claimed proteins may be derived, *inter alia*, from the same family of proteins or may be proteins of different structures and functions. An expression library can be created using any pool of DNA molecules. One skilled in the art would readily understand that reference to an expression library is related to a library for display of a wide variety of different peptides and proteins.

Regarding the term "protein:DNA," Applicants note that, with the present amendment, this term is replaced with the phrase "binding of the protein to the encoding DNA" thereby obviating this basis for rejection.

B) The Examiner alleges that the phrase "optionally present in more than one copy" as recited in claim 2 is indefinite. Applicants respectfully disagree that this phrase renders claim 2 indefinite. On the contrary, one skilled in the art will readily recognize that the single library member of claim 2 is a single library member expressed, i.e. a single protein species for display, per host cell or organism. That is, each library member is expressed in a separate host cell or organism. Within each individual host cell, expressing a single library member, there may be "more than one copy" of the nucleotide encoding that library member. Thus, Applicants submit that the phrase "optionally present in more than one copy" does not render claim 2 indefinite.

C) The Examiner objects to the term "modified" alleging that the metes and bounds of the claims is unascertainable. As a preliminary matter, Applicants point out that the term "modified" is only recited in claims 9 and 10. Thus, should the Examiner maintain the present basis for objection, Applicants request clarification as to the specific claims objected to.

Nonetheless, Applicants submit that it is clear from the context in which the term "modified" is used in claims 9 and 10 that this term is used in a manner consistent with the instant specification and with a meaning that would be readily understood by one skilled in the art. For example, at p. 11 is recited that "[I]n vitro translation allows the incorporation of many co- and post-translational modifications . . . ." Applicants submit that it would be clear, therefore, that "modified" encompasses, *inter alia*, both chemical and enzymatic modifications such as, for example, phosphorylation and sulphation, formation of disulfide bonds, glycosylation or isomerization, in addition to the incorporation of natural and/or non-natural amino acids. In claim 10, Applicants further submit that it is clear that the "modified" relates more specifically to replacement of tyrosine at amino acid position 450 of the P2A peptide or protein with phenylalanine.

D) The Examiner objects to the term "and/or" and the phrase "the relevant library member" as recited in claim 14. With the present amendment, claim 14 is amended to delete the phrase "and/or purifying" and to delete the term "relevant" thereby obviating this objection.

In view of the present claim amendments and accompanying remarks, Applicants respectfully submit that none of the instant claims are indefinite and request withdrawal of the bases for rejection under § 112, second paragraph.

Patentability under 35 U.S.C. §§ 102(e) or 103(a).

Claims 1, 6-9 and 11-18 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by or, alternatively, under 35 U.S.C. § 103(a) as allegedly obvious over Mattheakis et al., U.S. Patent No. 5,922,545.

Applicants respectfully traverse the stated grounds of rejection and submit that the instant claims are neither anticipated by nor obvious over Mattheakis.

Mattheakis relates generally to peptide expression libraries and, more specifically, to methodology whereby a polypeptide is linked via a tether segment to its encoding polynucleotide by a ribosome bound to a stalled polysome. Mattheakis does not describe any DNA binding proteins nor does this reference describe any proteins which bind to the encoding DNA through covalent binding of the protein to DNA as provided by the presently claimed invention.

The tether segments described in Mattheakis do not result in the binding of an encoding protein to its encoded DNA through covalent binding of the protein to DNA. The only reference to covalent binding is that between an immunoglobulin to mRNA serving as the translation template or to a cDNA copy thereof. This covalent binding is achieved by providing primers to which an immunologlobulin is covalently bound for production of the expression library itself. The mRNA or cDNA encodes an epitope which is recognized by the immunoglobulin. The encoded protein associates with its encoding mRNA or cDNA through binding of the epitope to the immunoglobulin bound to the nucleotide. The encoded protein does not bind to its encoding nucleotide through covalent bonding as presently claimed.

Other tether segments in Mattheakis include biotin/streptavidin specific binding pairs. As noted above, this is in contrast to the covalent binding of a peptide or protein to its encoding DNA as provided by the present invention.

In view of the present remarks in support of the patentability of the presently claimed invention, Applicants respectfully submit that none of the instant claims are anticipated by or obvious over Mattheakis and request withdrawal of the present basis for rejection under § 102(e) and § 103(a).

Patentability under 35 U.S.C. §§ 102(b) and 103(a).

Claims 1, 6-9 and 11-18 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by or, alternatively, under 35 U.S.C. § 103(a) as allegedly obvious over Gold WO 92/02536 [Gold I] or Gold WO 93/03172 [Gold II].

Applicants respectfully traverse the stated grounds of rejection and submit that the instant claims are neither anticipated by nor obvious over either of Gold WO 92/02536 [Gold I] or Gold WO 93/03172 [Gold II].

As discussed above, the instant claims are directed generally, *inter alia*, to methods, libraries, and DNA molecules for producing peptide or protein expression libraries. Libraries according to the present invention display diverse populations of peptides or proteins that are specifically associated with DNA encoding them through covalent binding of the protein to the encoding DNA.

In contrast to the methods, libraries and DNA molecules of the present invention, the cited references are directed to methodology wherein encoding mRNA remains attached to ribosomes. Gold I and Gold II do not teach or suggest methods involving DNA that binds to its

own encoded protein. On the contrary, Gold I and Gold II both rely on the interaction between mRNA and ribososmes. Translation is stopped or "stalled" so that an isolated ribosome complex includes at least one ribosome, one nascent peptide and the encoding mRNA. Gold I or Gold II do not describe the method involving binding of a protein to its encoding DNA. Indeed, by using ribosomes, the system relies on binding of ribosome to mRNA and the continued association of the encoded peptide to its mRNA via the ribosome.

On p. 9, line 14-19, Gold I refers to an "anchor" molecule which binds to the target molecule through a non-covalent interaction. *See, e.g.*, Gold I, Figure 7 (showing interaction through an enzyme-inhibitor or an enzyme-substrate). It is the "anchor" molecule that can be covalently linked, directly or indirectly to a bridge. Neither Gold I nor Gold II refer to DNA that encodes a protein which binds to its encoding DNA through covalent binding.

In view of these remarks, Applicants submit that the present invention is neither anticipated by nor obvious over Gold I or Gold II, and respectfully request withdrawal of the present bases for rejection under § 102(b) and § 103(a).

In view of the above claim amendments and remarks, Applicants submit that the claims are now in condition for allowance and request that the Examiner issue a Notice to that effect.

Respectfully submitted,

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Enclosures:
Postcard
Check; Form PTO/SB/17 (+ copy)
Abstract
Petition for an Extension of Time (+ 2 copies)

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